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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|-------------------------------|------------------|
| 10/070,387 | 03/06/2002 | Naoki Midoh | 2002-0317A | 2875 |
| 513 7590 01/27/2006 WENDEROTH, LIND & PONACK, L.L.P. 2033 K STREET N. W. SUITE 800 WASHINGTON, DC 20006-1021 | | | EXAMINER STEADMAN, DAVID J | |
| | | | ART UNIT 1656 | PAPER NUMBER |

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/070,387

Applicant(s)

MIDOH ET AL.

Examiner

David J. Steadman

Art Unit

1656

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 January 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: 1.
Claim(s) objected to: _____.
Claim(s) rejected: 13 and 15.
Claim(s) withdrawn from consideration: 2-12.


AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____.
13. ☒ Other: Note the attached Notice of References Cited (PTO-896).

Appendix A


David J. Steadman, Ph.D.
Primary Examiner
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ADVISORY ACTION

[1] Applicant's amendment to the claims, filed on 1/4/2006, is acknowledged and has been entered into the application. This listing of the claims replaces all prior versions and listings of the claims.

[2] The request for reconsideration of the claims is acknowledged. While the amendment overcomes the objection to the claims, the amendment fails to place the claims in a condition for allowance for the reasons stated below.

[3] The scope of enablement rejection of claims 13 and 15 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue the scope of variants of SEQ ID NO:2 as encompassed by the claims does not include a vast number, relying on Examples 9 and 10 of the Revised Interim Written Description Guidelines Training Material, Enzo Biochem, Inc. v. Gen-Probe Inc. 63 USPQ2d 1609, and Ex Parte Herrmann No. 2002-1630. According to applicants, there is no substantial variation within the scope of polypeptide sequences because the stringency of the recited hybridization conditions yields structurally similar molecules. Applicants argue that the stringent hybridization conditions would exclude the vast number of polypeptide variants as the corresponding nucleic acids encoding the variant polypeptides would not hybridize to SEQ ID NO:1 under the recited conditions. Applicants argue that hybridization and screening techniques were well-known at the time of the invention and only routine experimentation is required to make all variants as encompassed by the claims. Applicants further argue that the Office has issued numerous patents with

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claims reciting "stringent conditions" and "at least 95% homology," thus allegedly demonstrating the PTO's acceptance of such language.

Applicants' argument is not found persuasive. The examiner does not dispute that, at the time of the invention, methods of hybridization were known in the art. Further, the examiner acknowledges that the specification discloses an assay for determining whether an encoded protein has PF1022 synthetase activity (pp. 21-22). However, that hybridization was known in the art at the time of the invention and that the specification discloses an activity assay is insufficient to enable the full scope of the claimed invention. Contrary to applicants' position, the claims encompass a vast number of polypeptide variants. The specification discloses that "[a] cyclic depsipeptide synthetase according to the present invention is a protein comprising...a modified amino acid sequence of the amino acid sequence of SEQ ID NO:2 that has one or more modifications..." (p. 3, lines 16-23). Thus, In view of the disclosure of the specification, the examiner has interpreted claims 13 and 15 in accordance with MPEP 2111 as broadly encompassing any and all mutants and variants within the hybridization or identity limitations of the claims that have PF1022 synthetase activity.

The specification fails to provide even a single working example of a variant of SEQ ID NO:2 within the scope of the claim having PF1022 synthetase activity. While it is acknowledged that a working example is not required to demonstrate enablement, MPEP § 2164.02 makes clear that "[l]ack of a working example...is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." Further, the specification fails to provide guidance for altering the amino acid sequence

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of SEQ ID NO:2 with an expectation of obtaining a variant within the scope of the claims that has the desired activity/utility, *e.g.*, conserved and non-conserved regions and amino acids that are critical for the multifunctional catalytic activity. Based on the prosecution history, it is clear that the examiner is not requiring that applicant disclose every species encompassed by the claim. Instead, because of the high level of unpredictability associated with altering a protein's amino acid sequence, the specification should provide some guidance as to which variants of SEQ ID NO:2 would have the desired activity/utility and those that would not. For example, in *In re Wands* 8 USPQ2d 1400 (CAFC 1988), appellant presented data showing that, out of 9 cell lines that were screened, 4 of these cell lines produced the desired antibody, thus providing a skilled artisan with an expectation of success for obtaining a high-affinity monoclonal antibody. Also, in *In re Angstadt* 190 USPQ 214 (CCPA 1976), the specification disclosed at least 40 working examples of catalysts, one of which was not useful in the claimed method, thus providing a skilled artisan with some knowledge as to those catalysts that can or cannot be used in the claimed method. In this case, the specification provides no working examples of a variant of SEQ ID NO:2 having PF1022 synthetase activity and encoded by a nucleic having 95% identity to SEQ ID NO:1 nor does the specification provide guidance regarding knowledge as to those variants of SEQ ID NO:2 that are likely to have the desired activity, which is undisputed by applicant.

In this case, the functional effects of altering the sequence of a polypeptide are highly unpredictable, which is undisputed by applicant. The examiner has provided

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objective evidence (see, e.g., Branden et al., Witkowski et al., Seffernick et al., and Broun et al., all cited in the Office action mailed on 3/9/2005) of the high level of unpredictability in altering an encoding nucleic acid sequence with an expectation of obtaining an encoded polypeptide having desired activity/utility. This evidence is undisputed by applicants. Neither the prior art nor the specification discloses guidance regarding those nucleotides of SEQ ID NO:1 or amino acids of SEQ ID NO:2 that can be altered with an expectation of maintaining the ability to encode a polypeptide having the desired PF1022 synthetase activity. As the specification and prior art fail to provide guidance as to those nucleotides of SEQ ID NO:1 or amino acids of SEQ ID NO:2 that can be altered without disrupting the desired activity, a skilled artisan is left to randomly experiment to identify those polypeptides encompassed by the claims that have the desired activity/utility.

Regarding the breadth of parts (c) of claims 13 and 15, the examiner has used the well-known calculation of Meinkoth et al. (see, e.g., US Patent 6,057,491, particularly column 7, lines 32-41) to estimate that parts (c) of claims 13 and 15 encompass nucleotide sequences that are 85% identical to SEQ ID NO:1 (assuming that for each 1 degree Celsius the T_m is reduced from that calculated for a 100% identity hybrid, the amount of mismatch permitted is increased by about 1%). In the response filed on 1/4/2006, applicants request clarification as to the formula used in the calculation and how the examiner arrived at 85% identity using the calculation of Meinkoth et al. While the formula of Meinkoth et al. is well-known and commonly used in the prior art, the examiner provides the following clarification. At column 7, lines 32-41

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of the '491 patent, there is only a single disclosed formula, *i.e.*, $T_m = 81.5C + 16.6(\log M) + 0.41(\%GC) - 0.61(\%form) - (500/L)$. Definitions of the variables used in the disclosed formula can be obtained from the '491 patent. There are two chemicals that contribute to the molarity of monovalent cations in the recited hybridization solution, *i.e.*, trisodium citrate and sodium chloride. In a 1X solution, the molarity of these components is 0.195, 0.045 M from trisodium citrate and 0.150 M from sodium chloride. The number of G's and C's in SEQ ID NO:1 is 5296 (see Appendix A) out of total of 9633 nucleotides and the percentage of GC is 55%. There is no formamide in the hybridization buffer. Thus, applying these values for the variables gives an approximate T_m of 80.5 degrees Celsius. The temperature of hybridization in the claims is 60 degrees Celsius. The mismatch is reduced by 1% for every 1 degree Celsius decrease in T_m . Thus, at 60 degrees, the allowed mismatch is about 80.5-60% or 20%. Thus, nucleic acids with as little as 80% identity to SEQ ID NO:1 will hybridize under the recited conditions. Because this calculation is an approximation, the examiner erred on the conservative side, quoting a higher percentage identity of 85% in the prior Office action and will maintain the use of 85% herein. At 85% identity, one can alter up to 15% of the nucleotides of SEQ ID NO:1, which, according to the sequence listing is 9633 nucleotides. $0.15 \times 9633 = 1,444$.

Calculating the variability in a 95% identity limitation is more straightforward. In this case, at 95% identity, one can alter up to 5% of the nucleotides of SEQ ID NO:1, which, according to the sequence listing is 96333 nucleotides. $0.05 \times 9633 = 482$.

Thus, in order to make the full scope of recited polypeptides, one can simultaneously alter up to approximately 15% of the nucleotides of the sequence of SEQ ID NO:1, which is 1,444 nucleotides. While the breadth of parts (d) of claims 13 and 15 is more limited, at 95% identity to SEQ ID NO:1, the claim broadly encompasses simultaneous alteration of up to 482 nucleotides. As noted in a previous Office action, the resulting encoded polypeptide variants encompass those having a single amino acid substitution, addition, deletion, or insertion and any combination of amino acid substitutions, additions, deletions, and/or insertions up to the recited hybridization or identity limitation. In this case, the coding region of SEQ ID NO:1 is over 9500 nucleotides in length, encoding a polypeptide that is 3210 amino acids in length. Although the claims are not limited to variants having only a single amino acid substitution, in order to generate only *single* amino acid variants of each amino acid of SEQ ID NO:2, one must make 19^{3210} or 6×10^{4104} variants – just for *single amino acid variants*. This number was determined by recognizing that SEQ ID NO:2 is 3210 amino acids in length. Because there are 19 other possible naturally occurring L-amino acids that can replace each amino acid of SEQ ID NO:2, the number of possible variations is 19^n , where n = number of amino acids in a polypeptide.

Thus, for only *single* amino acid substitutions, the number of variants is 19^{3210} and the number becomes seemingly infinite when one considers that the claims broadly encompass simultaneous alteration of up to about 482 (parts (d) of claims 13 and 15) or 1444 nucleotides (parts (c) of claims 13 and 15) of the encoding nucleic acid sequence by substitution, addition, deletion, and/or insertion of a polypeptide that is 3210 amino

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acids. As SEQ ID NO:2 is encoded by 3210 codons and one can simultaneously alter up to 482 or 1444 nucleotides, at one nucleotide variation per codon, and assuming that each altered codon alters the corresponding amino acid, this allows for alteration of up to 15% or 45%, respectively, of the amino acids of the polypeptide of SEQ ID NO:2.

Based on this rough approximation, *the number of allowed permutations is astounding.*

While methods to produce variants of a known sequence, e.g., site-specific mutagenesis and random mutagenesis, are well-known to the skilled artisan, producing variants having PF1022 synthetase activity requires that one of skill in the art know or be provided with guidance for the selection of which of the *at least* 19^{3210} variants has the desired activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the at least 19^{3210} possible variants.

The reference of Guo et al. (*Proc Natl Acad Sci* 101:9205-9210; cited in the Office action mailed on 8/23/2005) teaches a study suggesting that the percentage of variants having multiple substitutions that maintain activity appears to be exponentially related by the simple formula: $(.66)^x \times 100\%$ (where x is the number of mutations introduced). As noted above, the claims broadly encompass a polypeptide that can have 15% or 45% of the amino acids altered, or another way of stating this is that the claims encompass polypeptides having 85% or 55% identity, respectively, to SEQ ID NO:2. Applying this estimate of 85% identity to SEQ ID NO:2 allows up to 482 mutations within the 3210 amino acids of SEQ ID NO:2 and thus only $(.66)^{482} \times 100\%$ or $1.0 \times 10^{-87} \%$ of random mutants having 85% identity to SEQ ID NO:2 would be active. Applying this estimate of 55% identity to SEQ ID NO:2 allows up to 1444 mutations within the

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3210 amino acids of SEQ ID NO:2 and thus only $(.66)^{1444} \times 100\%$ or $2.6 \times 10^{-259} \%$ of random mutants having 55% identity to SEQ ID NO:2 would be active. Thus, a significant number of variants must be screened in order to isolate those variants of SEQ ID NO:2 having the desired PF1022 synthetase activity. The art clearly *does not* typically engage in the screening of such a large number of variants to isolate those relatively few variants ($1.0 \times 10^{-87} \%$ or $2.6 \times 10^{-259} \%$) that would have the desired activity/utility, which is undisputed by applicants. That screening this number of variants is not routinely practiced in the art is further evidenced by Hult et al (*Curr Opin Biotechnol* 14:395-400), which teaches that recent attempts to randomly obtain variants of a given polypeptide included screening of "6000 transformants" (p. 396, left column, top) or 3.4×10^7 variants (p. 396, left column, bottom).

As such, based on a determination by weighing all of the factual considerations of In re Wands, the examiner has made a determination that the specification does not enable the claimed invention without undue experimentation.

It is noted that applicant's reliance on Examples 9 and 10 of the Revised Interim Written Description Guidelines Training Materials and *Enzo Biochem, Inc. v. GenProbe Inc.* appears to be misplaced as these address the issue of written description and not enablement. The claims are not rejected for a lack of adequate written description, but are instead rejected for lack of an enabling disclosure to make all polypeptides as encompassed by the claims. MPEP 2161 makes clear that "[t]he written description requirement is separate and distinct from the enablement requirement." Even applicant

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acknowledges this fact, by stating "the Guidelines deal with written description issues, as opposed to enablement" (instant response at p. 8, bottom).

Further, because each application is examined on its own merits, it appears that *Herrmann* does not apply here. Claim 6 of *Herrmann* was drawn to (in relevant part) a nucleic acid that hybridizes to SEQ ID NO:6 or a nucleic acid encoding SEQ ID NO:10. The hybridizing nucleic acid is not limited to having any specific biological activity. SEQ ID NO:6 of *Herrmann* is a 207 base pair nucleic acid and SEQ ID NO:10 of *Herrmann* is a 69 amino acid polypeptide. In a 1X SCC solution, the molarity of sodium is 0.195. The number of G's and C's in SEQ ID NO:6 of *Herrmann* is 92 out of total of 207 nucleotides and the percentage of GC is 44%. There is 50% formamide in the hybridization buffer. Thus, applying these values for the variables gives an approximate T_m of 64.8 degrees Celsius. The temperature of hybridization in claim 6 of *Herrmann* is 65 degrees Celsius. The mismatch is reduced by 1% for every 1 degree Celsius decrease in T_m . Thus, at 65 degrees, there is no allowed mismatch. In contrast to *Herrmann*, SEQ ID NO:1 of the instant claims is a 9,633 base pair nucleotide and the claimed variants are required to encode a polypeptide that has a defined biological activity. Further, there is substantial variation allowed in the hybridization conditions of claim 1 herein.

In response to applicants' argument that the PTO has sanctioned such hybridization language, applicants are reminded that each patent application is examined on its merits and the facts in each application vary sufficiently such that applicants cannot make a generalization that claims reciting "stringent conditions" or "at least 95% homology" are generally accepted by the Office.

The examiner has made every attempt to clarify the calculations used in arriving at the values discussed above. If applicant requests further clarification, applicant is requested to contact the examiner. Further, if applicant arrives at a different value or values than those noted above, applicant is requested to similarly provide a detailed description of such calculations.

[4] Status of the claims:

Claims 1-13 and 15 are pending.

Claims 2-12 are withdrawn from consideration.

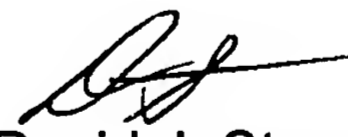
Claim 1 is in condition for allowance.

Claims 13 and 15 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs, 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

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APPENDIX A

ALIGNMENTS

RESULT 1

BD013055

LOCUS BD013055 9633 bp DNA linear PAT 02-AUG-2002

DEFINITION Cyclic depsipeptide synthetase and its gene and mass production system of cyclic depsipeptide.

ACCESSION BD013055

VERSION BD013055.1 GI:22093244

KEYWORDS WO 0118179-A/1.

SOURCE unidentified

ORGANISM unidentified

unclassified.

REFERENCE 1 (bases 1 to 9633)

AUTHORS Mido,N., Okakura,K., Miyamoto,K., Watanabe,M., Yanai,K., Yasutake,T., Aihara,S., Futamura,T., Kleinkauf,H. and Murakami,T.

TITLE Cyclic depsipeptide synthetase and its gene and mass production system of cyclic depsipeptide

JOURNAL Patent: WO 0118179-A 1 15-MAR-2001;
MEIJI SEIKA KAISHA LTD,NAOKI MIDO,KAORU OKAKURA,KOICHI MIYAMOTO,
MANABU WATANABE,KOJI YANAI,TETSUYA YASUTAKE,SATO AIHARA, AKAFUMI
FUTAMURA, HORST KLEINKAUF,TAKESHI MURAKAMI

COMMENT OS Mycelia sterilia

PN WO 0118179-A/1

PD 15-MAR-2001

PF 07-SEP-2000 WO 2000JP006103

PR 07-SEP-1999 JP 99P 253040,06-APR-2000 JP 00P 104291 PI

NAOKI MIDO,KAORU OKAKURA,KOICHI MIYAMOTO,MANABU WATANABE, PI KOJI
YANAI,

PI TETSUYA YASUTAKE,SATO AIHARA,TAKAFUMI FUTAMURA,HORST

KLEINKAUF,

PI TAKESHI MURAKAMI

PC C12N9/00,C12N15/52,C12N1/15,C12P21/04

CC peptide synthetase for PF1022

FH Key Location/Qualifiers

FT CDS (1)..(9633)

FT mat_peptide (13)..(9630).

FEATURES Location/Qualifiers

source 1..9633

/organism="unidentified"

/mol_type="genomic DNA"

/db_xref="taxon:32644"

BASE COUNT 2318 a 2834 c 2462 g 2019 t

ORIGIN

Alignment Scores:

| | | | |
|------------------------|----------|---------------|------|
| Pred. No.: | 0 | Length: | 9633 |
| Score: | 16544.00 | Matches: | 3210 |
| Percent Similarity: | 100.00% | Conservative: | 0 |
| Best Local Similarity: | 100.00% | Mismatches: | 0 |
| Query Match: | 100.00% | Indels: | 0 |
| DB: | 6 | Gaps: | 0 |